Eye (2003) 17, 369–384

www.nature.com/eye

CLINICAL STUDY

Visual function in the brain-damaged child

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Abstract

The essential role of the primary visual cortex in visual processing has been extensively studied over the last century or more. Injuries to the visual cortex in adult humans can produce blindness, referred to as 'cortical blindness'. In children some degree of visual recovery has been noted in comparable injuries and for that reason the term 'cortical visual impairment' has been suggested as a more appropriate diagnosis in children. This term is, however, inaccurate as a significant number of children with visual loss and neurologic damage have injuries to the noncerebral pathways (for example—optic radiations in children with periventricular leukomalacia). In this study we compare visual outcomes and recovery in children with primary visual cortex lesions *vs* those with periventricular leukomalacia. We suggest that the poorer outcomes of children with periventricular leukomalacia could have been predicted based on studies of the mechanisms of visual recovery in infant animals following visual cortex ablation.
Eye (2003) **17,** 371–386. doi:10.1038/sj.eye.6700364

Notion of 'visual cortex'

The notion that specific localized portions of the cerebral cortex subserve only visual functions is a relatively recent development in neuroscience.[1–4] During the 17th century, scientists became interested in detailing the pathway of the optic nerve fibres. Most of these interests centred on a single question: What course do the fibres of the optic nerve take through the chiasm? During the Middle Ages and the Renaissance, the consensus of educated opinion was that optic nerve fibres do not decussate but remain entirely ipsilateral throughout their course. Sir Isaac Newton[5] challenged this opinion in a short, less than a page in length, query at the end of his book on 'Opticks'. Newton deduced that some optic nerve fibres had to cross in the chiasm in order to produce a stereoscopic image.

Subsequent investigators began to ask a second question: Where do the fibres of the optic nerve ultimately terminate? Thomas Willis followed the optic nerve fibres through the chiasm to the brainstem and striate nuclei and insisted that these were the ultimate structures in the visual process.[6] In contrast, Raymond Vieussens[7] suggested that the optic nerves ultimately terminate in the cerebral cortex. I shall quickly pass over the provocative proposal of the Rene Descartes[8] that optic nerve fibres terminate in the ventricle and the images of the two eyes merge in the pineal body. Yet, we should note that Descartes might have been the first to suggest that the fibres of the optic nerves and the terminals are topographically organized.

Herman Boerhaave described a rather bizarre case that supported a cortical role in vision.[9] He described a Parisian pauper whose calvarium had been removed. The pauper used it to collect alms. For a small payment, the pauper would allow people to touch his brain. This occasionally elicited visual sensations—often flashes of light followed by a short period of blindness.

It was not until the early 19th century that many scientists began to suggest that vision was served by its own specific portions of the cerebral cortex. Ironically, many of these first advocates of function-specific localization in the brain had been trained as phrenologists. In Italy, Bartolomeo Panizza[10] had been influenced by phrenology and he suggested that visual projections include the thalamus and ultimately the posterior portions of the cortex. Panizza's thesis was based both on human pathological studies and ablation experiments in dogs. Panizza's voice was largely ignored since accepted doctrine was that while visual fibres did go to the thalamus they went no further. This view held that the visual 'centre' resides

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Received: 7 August 2002

entirely in the thalamus.[11] Furthermore, his work was published in Italian and largely ignored in the leading medical centres in England, France, and Germany.

The work of Albrecht von Graefe[12] could not be ignored. He had established in 1852 one of the leading eye clinics in Europe. When he was 26 years old, he founded the Archiv für Ophthalmologie. Two years later, in 1856, he published therein his findings on early attempts of visual field testing in patients. The sophistication of his technique was not noteworthy but he correctly observed that patients with homonymous hemifield defects were often patients with posterior cortical lesions.

Early in the 19th century, Marie-Jean Pierre Flourens[13] conducted some of the first laboratory studies to suggest that the cerebral cortex plays an essential role in visual perception. He did not conclude, however, that specific cortical locations subserve distinctly different functions. His studies were based on observations of birds after one cerebral cortex was lesioned. The full significance of his work was not fully appreciated until many years later.

It was in the last half of the 19th century that the laboratory studies of David Ferrier[14–18] in London and Hermann Munk[19] in Berlin firmly established that the occipital cortex is essential to visual functions. David Ferrier,[15] a physiologist at King's College Hospital initially came to the erroneous conclusion that the angular gyrus and the occipital cortex are equally important in normal visual functions. In subsequent experiments, he found that bilateral angular gyrus ablations did not cause complete blindness whereas destruction of the occipital lobes did.[16] His experiments were essential in establishing the primary role of the occipital cortex in visual function.

At the Seventh International Medical Congress in 1881 in London, he confronted the German physiologist, Friedrich Goltz, who was convinced that the cerebral cortex was not divided into functionally specific loci.[20] At the Royal Institute, these two scientists each presented animals that had undergone experimental cortical ablations, and discussed the implications of their findings.[21] Goltz insisted that he had performed many experiments on dogs and even after large ablations of the cerebral cortex, they did not become blind, deaf or paralysed. To highlight his argument, he stated that he had brought one of his dogs with him. He insisted that both parietal and occipital lobes had been excised, but the dog showed no specific disability resulting from these lesions. Ferrier countered by insisting that his experiments led him to believe that vision, hearing, smell, touch, and taste all have their specific cortical representations. He described a monkey that was unable to move its limbs on the right side 7 months after its 'motor' cortex had been removed. The following day both animals were examined and their behaviour confirmed what each man had described. However, when the animals were killed, the lesions in the dog were found to be much less extensive than Goltz had indicated. This accounted for the apparent minimal disability suffered by the dog. In contrast, the lesion in the monkey was found to be just as Ferrier had reported—in the area of the rolandic fissure.[22] Regrettably, this very public victory led to a serious legal problem for Ferrier. Three months after the International Medical Congress, Ferrier was charged with violating the Cruelty to Animal Act of 1876. After much adverse publicity, Ferrier was acquitted of the charges.[23]

Hermann Munk[19] studied the effects of brain lesions on both dogs and monkeys. Unlike Goltz and Ferrier, he performed long-term functional examinations on his animals, sometimes up to 5 years after the cortical lesions were performed. He concluded that only the occipital cortex is responsible for visual function. It is essential to note that Munk specifically stated that upon recovery from occipital lobe ablations, dogs are unable to recognize objects but are capable of walking around and avoiding them. He called this visual ability, 'Seelenblindheit' or 'psycic blindness'. His description of such a dog is dramatic:

'He remains completely cold when looking at people which he used to greet with joy; he remains just as cold in the presence of dogs with which he formerly used to play. As hungry and thirsty as he may be, he does not look as formerly to those places in the room where he used to find his food and even if one puts his food and water right in his way, he frequently goes around them without paying any attention to them. Finger and fire approaching the eye do not make him blink. The site of the whip, which used to drive him regularly into the corner, does not frighten him any more in the least.'[19] It is a gripping description but our interpretation of the nature of the residual function in these animals may be different from Munk's in the light of more recent experiments to be described in the final section. It is also important to emphasize that Munk reported that dogs recovered additional visual function after several weeks of recovery from the experimental surgery.

Munk's findings were confirmed by the Italian scientist, Luigi Luciani.[24] Munk's perception that the occipital cortex is the primary visual cortex gained support from the work of Edward Schäfer[25–28] at the University College, London. Schäfer presented his studies performed on monkeys. Schäfer lesioned the angular gyrus and the occipital cortex. In his 1887 presentation to the Royal Society, he argued that the occipital cortex was the primary visual structure and not the angular gyrus.[28] Ferrier challenged Schäfer about the

importance of the occipital cortex in vision and Schäfer countered that Ferrier's lesions had been incomplete, thus leading to the erroneous conclusion that the angular gyrus was the primary cortex site of visual function. Moreover, he challenged Munk about the cortical localization of macular function.[27] Munk had concluded that the posterior dorsal area of the occipital cortex subserves macular function in the dog. Schäfer correctly concluded that central visual function in monkeys and man is represented on the mesial surfaces of the occipital cortex. Moreover, in contrast to Munk's findings in dogs, Schäfer reported, 'that removal of both occipital lobes produces total and permanent blindness'.[28] The species-specific difference in recovery from occipital cortex injury was thus already apparent.

More details about how the visual radiations project to the visual cortex were provided by the studies of myelogenesis by Paul Flechsig.[29] Flechsig,[30] a professor in Leipzig, initially proposed that the visual radiations projected from the superior colliculus, the pulvinar, and the lateral geniculate body. He later asserted that they arose only from the lateral geniculate body. Grafton Elliot Smith,[31,32] an Australian, studied both human and other primate occipital cortex morphology and reached similar conclusions about the visual radiations projecting to the occipital cortex.

Clinical observations soon supported the role of the occipital cortex in visual function. Herman Wilbrand,[33,34] in Hamburg, studied patients with brain injuries and concluded that vision was localized to the occipital cortex. Similar findings were reported by the American, Moses Allen Starr.[35–37] Salomon E Henschen,[38,39] a Swedish scientist, reviewed more than 160 cases of recorded instances of blindness and hemifield defects resulting from cerebral injury. His material led him to conclude that the human visual cortex is limited to the area around the calcarine fissure and that lesions of the angular gyrus (or posterior parietal lobe) gave rise to visual defects only if the optic radiations were involved.[40,41]

The First World War provided an unwanted opportunity for the Irish neurologist, Gordon Holmes,[42,43] to study the results of occipital cortex damage in men. Holmes carefully mapped the visual field loss of men whose injuries affected the posterior pole of the cortex. Holmes confirmed that a tiny area of damage in this portion of the cortex produced a discrete scotoma in the visual field. Holmes, however, insisted that unlike Munk's dogs who demonstrated some residual vision after visual cortex removal, the scotoma produced by visual cortex damage in the soldiers he studied was 'fixed and immutable'.[42] Holmes went on to remeasure these scotomata for many years and found they did not change. This permanence of visual loss associated with visual cortex damage in men would not be challenged until a half century later with the introduction of the controversial notion of 'blindsight'[44–47] (an issue to be discussed at length in a later section). It seems only appropriate to bring this historical section to a close by noting that Gordon Holmes delivered the Ferrier Lecture in 1944. His talk was entitled, 'The Organization of the Visual Cortex in Men'.[43]

The clinical problem and its importance

The term 'cortical blindness' is used to refer to the patient who has been rendered blind by bilateral damage to the occipital cortex. It is a term introduced as the result of studies of adult patients.[48] Cortical blindness is defined clinically as a bilateral loss of vision with normal pupillary responses and an eye examination, which shows no abnormalities.[49,50] In adults, this is considered to be an infrequent event and usually the result of arterial circulatory disease.[51]

For several reasons, the term 'cortical blindness' does not seem appropriate to describe the clinical conditions responsible for visual loss due to damage to the occipital cortex and its associated structures in children.[49,50,52,53] First and foremost, total absence of sight in children caused by a bilateral disturbance of the optic radiations and/or calcarine cortex is extremely rare.[50,54–60] Moreover, unlike the case in adults, significant visual recovery can be documented in a large proportion of the children with visual loss caused by calcarine cortex injury. Roland *et al*[56] studied 30 children with visual loss caused by occipital cortex injury and documented some degree of visual recovery in 50%. In a study of 19 babies with perinatal hypoxic-ischaemic insults, Casteels *et al*[57] demonstrated that 16 of them could be documented to have improved visual function over a 3–7 year follow-up. Recently, Huo *et al*[61] reported on a series of 170 children with visual loss caused by optic radiation and/or visual cortex damage from a number of different causes. In this study, 60% of children showed some visual recovery. For these reasons, the term, 'cortical visual impairment' was introduced to emphasize the visual potential in these neurologically damaged children.[49,50]

The term 'cortical visual impairment' is unfortunately equally misleading in describing many of these children. It fails to accurately describe the group of children with visual impairment resulting from primarily deep subcortical white matter insults (periventricular leukomalacia). For this reason, the term 'cerebral visual impairment' has been suggested as a replacement for 'cortical visual impairment'. This problem surrounding a precise terminology to describe children with visual impairment caused by neurologic disease has been

compounded by some who would use the term 'cortical visual impairment' to describe children with ocular motor apraxia, saccadic paralysis, visual inattention, etc.[62,63] There is an obvious need for the establishment of an international classification of neurologic visual disorders. For the purpose of this presentation, I will continue to use the widely accepted term 'cortical visual impairment' despite its imprecision in some cases.

Following the studies of Holmes documenting cortical damage resulting in visual loss in adults (soldiers) cortical visual impairment was infrequently reported in children. Most of the cases were a result of meningitis and/or encephalitis or hydrocephalus. The most common organism responsible for meningitis and cortical visual impairment is *Hemophilus influenza*.[64,65] The onset of neurological visual loss associated with meningitis may be late and usually occurs after the child has recovered from the acute infection. Thrombophlebitis[64,66,67] and arterial occlusion[68,69] play a prominent role in the pathophysiology of cortical visual impairment associated with meningitis. Encephalitis, especially the cases due to neonatal herpes simplex infection, may cause cerebral visual impairment.[70]

Hydrocephalus can cause acute and chronic cortical visual impairment.[71–73] With significant dilation of the ventricles and the resulting distention of the posterior cortex, occlusion of the posterior cerebral arteries and resulting occipital cortex infarction may occur.[74] However, most cases of cortical visual impairment associated with hydrocephalus are not associated with infarction of the occipital cortex but simply dilation of the ventricles. Long-term shunt malfunction can cause permanent cortical visual impairment.[72] Ironically, cortical visual impairment may occur following a successful shunt procedure, presumably due to too rapid correction of the elevated intracranial pressure.[75]

Cortical visual impairment may occur secondary to a variety of other causes including hypoglycemia,[76] haemodialysis,[77] cisplatin therapy,[78] seizures,[79] cerebral arteriography,[80,81] malaria,[82] and neurodegenerative disorders. Trauma may produce either a transient[83,84] or a permanent[85] form of cortical visual impairment. It is a tragedy that 'nonaccidental' trauma is increasingly seen as a significant cause of cortical visual impairment in all societies.

However, a single cause accounts for the overwhelming majority of cases of cortical visual impairment in children-perinatal hypoxic-ischaemia.[59–61,86] With advances in perinatal care has come increased survival rates for children with hypoxic-ischaemic insults.[55,59,87] Indeed, the increasing prevalence of cortical visual impairment in many ways parallels the resurgence of retinopathy of prematurity as a cause of visual impairment in children in developed countries.[61] In San Francisco, over 50% of the visually impaired children referred for preschool services have cortical visual impairment, and nearly 20% have retinopathy of prematurity.[61]

Cortical visual impairment is now clearly the single greatest cause of visual impairment in young children in developed countries.[87–91] Cortical visual impairment places a major burden on ophthalmological and educational services in these countries. Moreover, cortical visual impairment is rarely an isolated defect as the vast majority of affected patients have associated neurological or ophthalmological defects. In the study by Huo *et al*,[61] 75% of the children had associated neurological deficits, many of which require on-going management and some of which may actually interfere with visual functioning (eg seizures and anticonvulsant therapy). In this study, over 50% of the patients with cortical visual impairment had seizures. A significant number of these patients are afflicted with cerebral palsy or other motor deficits. Huo *et al* documented that over 40% of their patients had significant neurological deficits affecting mobility. In the study by Rogers *et al*,[87] 53% of the patients with cortical visual impairment had cerebral palsy. In a study from Hong Kong, Wong[92] reported that 100% of congenital and 88% of acquired cortical visual impairment patients had associated neurological abnormalities. The results of this can be seen by visiting any residential blind school in the developed world where the vast majority of students are now multiple handicapped, and the teaching strategies developed for children with visual impairment caused by isolated ocular disease are found not to be appropriate or effective for these children with cortical visual impairment.[93–96]

Pathophysiology of hypoxic-ischaemic brain injury in preterm and term infants

It is essential to understand the pathophysiology of hypoxic-ischaemic brain injury in neonates when discussing cerebral visual impairment. First, as has already been stated, hypoxic-ischaemic brain injuries are the most common cause of cortical visual impairment in children. Yet, equally important and often ignored is the fact that several distinctly different patterns of brain injury can result from hypoxic-ischaemic insults depending on the child's age, severity of hypoxia, and duration of hypoxia.[97–101] These different patterns of injury result in different clinical manifestations of cortex visual impairment and, I believe, strikingly different prognoses for recovery due to involvement or sparing of specific neural structures.

That hypoxia is usually the initiating stimulus in the sequence of events leading to brain injury in the

asphyxiated child is well established.[102–104] However, hypoxia is not the primary factor in producing the actual brain damage. Hypoxia and the accompanying hypercarbia result in a loss of the normal vascular autoregulation in the brain. This, in turn, leads to pressure-passive blood flow.[105] Ordinarily, blood vessels of the brain constrict when the blood pressure increases and dilate when the blood pressure decreases. This process helps maintain a relatively constant blood flow in the brain. Thus, hypoxia precipitates a reduction in systemic blood flow that is then coupled with a loss of autoregulation of cerebral blood flow. These are the factors that led to decreased perfusion of the brain.[106,107] It is this resulting hypoperfusion of the brain that initiates the actual brain damage. It should be noted that the newborn brain is extremely resistant to hypoxic damage in the setting of normal cerebral blood flow. This is because glucose and other available energy substrates can prevent brain damage, at least in the short term.[108] In addition to the loss of vascular autoregulation, hypoxia alters capillary permeability, and with reperfusion these capillaries may bleed leading to intracerebral or intraventricular haemorrhage.[109,110] The minimum duration of hypoperfusion necessary to produce brain damage in human infants is not yet conclusively established. However, in experimental infant animal models, 7–10 min of hypoperfusion results in some brain damage.[111,112]

A mild to moderate reduction in cerebral blood flow in the newborn infant leads to a shunting of blood from the anterior circulation to the posterior in order to maintain normal flow to the life-essential structures in the brainstem, basal ganglia, and cerebellum.[113] In this situation, the resulting brain damage is concentrated in the intervascular zones (watershed areas) of the cortex. However, in severe hypoperfusion conditions, the shunting mechanism is apparently inadequate to protect these vital deeper brain structures.[114,115] Indeed, in this situation the initial injuries are concentrated in the thalami and brainstem, and only later in the process does damage occur to the cortex and subcortical white matter.[98,116,117]

The mechanisms responsible for these specific patterns of selected brain damage are not completely understood. However, at least two possible mechanisms have been suggested. The first postulates that the patterns of brain injury are related to the relative regional energy requirements of the brain at the time of injury.[120] It is well known that regions of the brain undergoing myelination show greater metabolic activities than those not yet myelinated.[118–120] MRI studies of newborns who suffer significant hypoperfusion injuries consistently show a close correlation between the normal patterns of age-related myelination and the sites of brain injury.[101,120–122]

A second theory suggests that the pattern of brain injury in hypoxic-ischaemic encephalopathy is related to the distribution of *N*-methyl-D-asparate (NMDA) receptors.[123,124] This theory asserts that the brain damage associated with hypoxia and hypoperfusion is primarily because of the release of excessive excitatory amino acids, primarily glutamate.[125] Neurons with NMDA receptors will be the primary ones affected by the release of glutamate and the chain of chemical events it induces that led to cell death. Thus, the pattern of brain injury is determined by the concentration of NMDA receptors, which varies during different stages of brain development.[124]

Most important to clinicians is the fact that no matter what the pathophysiologic explanation may be, the patterns of brain injury resulting from hypoxia and hypoperfusion are affected by the postconceptional age of the child. Full-term infants will sustain injury primarily at the watershed zones of the cerebral cortex with minimal damage to the periventricular white matter. In sharp contrast, premature infants who sustain a comparable hypoxic-hyperfusion event will undergo significant periventricular injury with little or no cortical damage. An age-related change in location of the intervascular boundary zones has been cited as the main reason for this marked difference in injury pattern depending on the infant's age.[126,127] It is suggested that ventriculofugal blood vessels in the brain are poorly developed in the premature infant. Thus, entire blood supply to the cortex as well as the subcortical areas is dependent on the ventriculopetal blood vessels penetrating from the surface of the brain. An additional factor in the tendency for the periventricular area to be damaged in premature infants is that this region responds to hypoxia differently than the cortex. It uses anaerobic glycolysis, which results in a tissue-damaging acidosis.[128] Some degree of periventricular white matter damage is a common finding on imaging studies of premature infants who survive a hypoxic-hypoperfusion injury. It is especially common in those premature infants with hyaline membrane disease, hypocapnia, twin pregnancy, septicaemia, or ischeamia.[99,129,130]

Patterns of injury on neuroimaging studies of children with cortical visual impairment

Several types of brain injury may occur in premature infants owing to a mild to moderate episode of hypoxia and hypoperfusion. These included periventricular leukomalacia, periventricular haemorrhagic infarction, germinal matrix haemorrhage, intraventricular haemorrhage, and cerebellar infarction.[129] However, I will limit this discussion to injury of the periventricular white matter—the most common site of brain injury

related to hypoxia-hypoperfusion in premature infants.[106,107,130] The corticospinal tracts run through the periventricular region and for this reason, impaired motor function is the most common sequela of periventricular white matter injury. Spastic diplegia, weakness of the lower extremities, is the most common neurologic disability in premature infants with an incidence of 5–15%.[131] Visual impairment is quite common in premature children with spastic diplegia, with the incidence as high as 70%.[132,133] These children almost invariably have some form of periventricular leukomalacia.

As a result of the difficulty involved in transporting and caring for very sick premature infants, CT and MRI are not usually used in the early evaluation of these patients. The initial studies are usually ultrasonograms. However, once the infant has been discharged from the hospital, MRI and CT are more useful and accurate than ultrasonogram in assessing the extent of subcortical white matter damage and associated pathologies. CT and MRI studies of these patients may demonstrate: (1) ventriculomegaly with an irregular outline of the body and trigone of the lateral ventricles, (2) reduced volume of periventricular white matter, and (3) deep, prominent sulci that abut or nearly abut the ventricles with little or no interposed white matter.[134,135] In addition, MRI will show increased signal intensity in the area of the periventricular white matter and delayed myelination.[57,136] It is especially important to note that sagittal MRI may reveal thinning of the corpus callosum owing to degeneration of the transcallosal fibres.[137,138]

An entirely different pattern of brain injury is seen in premature infants who have suffered a profound hypotensive event or cardiopulmonary arrest. Injury is concentrated in the deep grade matter and brainstem nuclei, although some periventricular damage may occur as well.[101,114] The brainstem, cerebellum, and thalami are predominately injured. An MRI performed several months after injury will reveal small thalami, brainstem, and cerebellum, often accompanied by reduced cerebral white matter.[97] The survival rates for this group are poor but, if they survive, they may present with athetosis in addition to quadraparesis, severe seizure disorder, and mental retardation.[56]

As a result of improved survival rates of very premature infants,[139] periventricular leukomalacia is seen with increasing frequency as a cause of cortical visual impairment.[104,140] In contrast, the incidence of encephalopathy secondary to hypoxic-ischaemic injury in term infants appeared to be decreasing.[141] Nevertheless, 10–15% of cerebral palsy is secondary to perinatal hypoxic-ischaemic injury in term infants.[142,143]

The primary injury in term infants who suffer a mild to moderate hypoxic-hypoperfusion event occurs at the watershed areas, the regions between the middle and posterior cerebral arteries and between the anterior and middle cerebral arteries. This results in discrete, often cystic, infarctions in the boundary zones between the major vascular territories. Thus, infarction is most likely to occur in the frontal and the parieto-occipital regions. In the acute phase of injury, neither ultrasound nor CT studies are accurate in delineating the extent of injury[144,145] MRI is, therefore, preferred in evaluating these patients. After the child has recovered from the acute hypoxic-ischaemic insult, MRI studies may reveal (1) cortical thinning and diminution of the underlying white matter in the area of infarction, (2) *ex vacuo* dilation of the lateral ventricles, (3) the development of a gyral anomaly, ulegyria, due to the pattern of shrinking cortex, and (4) wedge-shaped infarction in the watershed zones.[146]

A distinctly different pattern of brain injury is seen in term infants who suffer a profound hypoxic-hypoperfusion event or cardiocirculatory arrest. Most of these children however do not survive.[147,148] Injury occurs primarily in the lateral thalami, posterior putamina, hippocampus, and corticospinal tracts.[101,149,150] It is essential to know that many of these children will also show significant injury to the lateral geniculate bodies and the optic radiations. The cortex is usually spared except for the peri-Rolandic gyri.[101]

From the point of view of ophthalmologists evaluating children with cortical visual impairment, it is primarily the premature infants with periventricular leukomalacia and the term infants with infarction of the striate cortex who are of interest. First, both groups reveal significant damage to important visual structures. Second, the neurological consequences of profound hypoxia and ischaemia in premature and term infants are so devastating that visual assessment is often nearly impossible although no less important. Third, the survival rates for profound hypoxic-ischaemic episodes in preterm or term infants remain poor.

The clinical profile and visual prognosis of the child with periventricular leukomalacia and infarction of the visual cortex

Most studies of cortical visual impairment have described the clinical characteristics of the patients and their visual outcomes as if they were a homogeneous group of patients.[49,50,56,61] The previous discussion should have made clear that nothing is further from the truth. There are multiple aetiologies of cortical visual impairment in children. There are also distinctly different areas of the brain damaged as a result of these different aetiologic factors. Moreover, in the case of hypoxic-ischaemic insults, the pattern of neurologic

damage is very different depending upon whether the infant was born preterm or at term.

A few recent studies have attempted to comment on differences in visual outcomes in children with different patterns of brain injury.[56–60] Cioni *et al*[58] evaluated patients with cortical visual impairment with Teller acuity cards and MRI studies. They evaluated 42 infants with injury primarily to the optic radiations and 19 with visual cortex damage. Although there was significant variation within each study group, they concluded that damage to the optic radiations as shown on MRI studies was a better predictor of poor visual function than injury to the visual cortex. However, the patients were only evaluated once in early infancy and no attempt was made to establish whether visual improvement occurred over time. Eken *et al*[60] studied 65 at-risk infants with Teller acuity cards and MRI or CT scans. They concluded that poor visual function was correlated with either extensive periventricular white matter damage or striate cortex infarcts. They did not indicate whether one pattern of insult or the other was associated with a poorer visual outcome. No follow-up data were provided. Mercuri *et al*[150] conducted a short-term study of 31 term infants who had suffered a hypoxic insult. A total of 20 infants had poor visual function as measured by Teller acuity cards and all of these had damage to the visual cortex on MRI studies. The poorest visual function was measured in infants with injuries to both the visual cortex and the basal ganglia. It is unfortunate that they did not compare these findings to a comparable study group of preterm infants.

At the University of California San Francisco, a group of us in the departments of Neurology, Neuroradiology, and Ophthalmology have been interested in the questions surrounding visual impairment and the possibility of visual recovery in children with neurologic damage. We have undertaken, therefore, a retrospective review of children seen with a diagnosis of cortical visual impairment seen in our Paediatric Ophthalmology unit. The review included the records of all patients seen between 1979 and 1994. We reviewed approximately 7200 records.

At the time of the child's initial appointment, a diagnosis of cortical visual impairment was made if there was (1) visual loss in the absence of signs of anterior visual pathway disease or (2) vision loss exceeding that, which was expected given the findings of the ocular examination. Patients with cortical visual impairment and coexisting retinopathy of prematurity affecting macular function were excluded from this study. Children with nystagmus underwent electroretinographic testing (ERG) and we carefully excluded all children whose poor visual function could be attributed entirely to noncentral nervous system deficits. All patients underwent at least one MRI or CT study.

Review of the patient records revealed 170 cases of cortical visual impairment, 2.4% of the total number of patients seen during the study. Although our Paediatric Ophthalmology unit has a specific interest in neuro-ophthalmology, this figure reemphasizes that cortical visual impairment is a major cause of visual disability in children. We were interested in those children with cortical visual impairment who were seen on more than one occasion. A total of 96 patients were identified to have been examined by us two or more times. The average length of follow-up for this group was 5.9 years with a range of 9 months to 15 years. We identified several major causes of cortical visual impairment in these children. The most common aetiology was perinatal hypoxia (22.4%). Cerebral vascular accidents accounted for 14% and meningitis/encephalitis for 12.4%. Next in frequency were acquired hypoxia (10%), hydrocephalus (9.4%), and prematurity (7.7%). Less frequent aetiologies included intracranial cyst (5.3%), head trauma (4.1%), seizures (4.1%), and brain tumours (2.9%). *In utero* drug exposure accounted for 1.8% of cases. In 9.4% of cases we were unable to establish the aetiology.

For the purpose of this study, we determined whether the major damage in each child was primarily in the visual cortex or the periventricular white matter based on CT or MRI studies. Of the 96 children who had been examined on more than one occasion, 41 were found to have primary striate cortex damage. In 26 patients, the damage was primarily to the periventricular white matter without significant striate cortex damage. The remaining 29 patients either had (1) extensive diffuse brain injuries, (2) significant damage to both the optic radiations and striate cortex, or (3) normal MRI or CT studies. We excluded these 29 patients from the study.

Although some of the patients had undergone visually evoked potential studies (VEPs), we wished to assess each patient with a functional evaluation of their vision. For this study, we devised a functional evaluation of vision with the following six levels of visual function

- Level I was if the child could only perceive light at the time of the examination.
- Level II was if the patient could occasionally visually fixate on large objects, faces, or movement in the environment.
- Level III was if visual function was highly variable, but with at least some moments of good visual fixation as indicated by: (1) the ability to see small objects (such as coins or stickers) or (2) could reliably visually fixate a face.

Table 1 Initial level of visual function for the study group

Initial vision (levels)	*Description of visual function*	*Patients with striate cortex damage*	*Patients with periventricular white matter damage*
1	Light perception only	9 (22.2%)	10 (38.4%)
2	Occasional fixation on large objects	20 (48.7%)	13 (50%)
3	Occasional fixation on small objects	8 (19.4%)	2 (7.6%)
4	Reliable fixation on small objects 6/36–6/60	3 (7.3%)	1 (3.8%)
5	Reliable visual acuity 6/18–6/36	1 (2.4%)	0
6	Completely normal vision	0	0

- Level IV was if a patient could reliably fixate on small targets and/or with visual acuity that could be measured in the range of 6/36–6/60.
- Level V was if there was good reliable fixation and/or with visual acuity (measured under binocular viewing conditions) of 6/18–6/36.
- Level VI was if there was a completely normal sensory visual examination.

The initial levels of vision for the two groups (group 1 with striate cortex injury and group 2 with periventricular white matter damage) are shown in Table 1. For group 1 (striate cortex injury), 22.2% were at level I, 48.7% at level II, 19.4% at level III, 7.3% at level IV, and 2.4% at level V. None were at level VI. For group 2 (periventricular white matter damage), 38.4% were at level I, 50% at level II, 7.6% at level III, and 3.8% at level IV. None were at level V or VI. While it is true that patients with periventricular leukomalacia were more likely to be at level I (38.4%) than those with striate cortex damage (22.2%), the overall distribution of initial acuity levels of the two groups was remarkably similar. This is in contrast to the finding of Cioni *et al*[58] who found that infants with periventricular white matter injury involving the optic radiations were more likely to present with poorer visual function than those who suffered an injury to the striate cortex. This difference may be because the patients in our study had been referred to our clinic as they appeared to have poor vision, whereas Cioni *et al* screened a group of brain-injury infants independent of whether they had poor visual function.

We were then interested in whether or not these two groups of children revealed any improvement on subsequent examinations. The change in visual function was based on the level of visual function on the last examination compared to the level of the initial examination. The changes in levels of visual function of these two groups of children are shown in Table 2. In group 1 (striate cortex injury), 21.9% showed no improvement, 43.9% improved one level, 26.8% improved two levels, 4.8% improved three levels, and 2.4% improved four levels. No child improved five levels. In group 2 (periventricular white matter injury), 57.6% showed no improvement, 30.7% improved one level, 7.6% improved two levels, and 3.8% improved three levels. None of these children improved four or five levels. Thus, 78% of children with striate cortex damage showed at least one level of visual improvement, whereas only 42% of those with periventricular white matter injury showed at least one level of visual improvement. Moreover, in the children with striate cortex damage (group 1), 34% improved more than one level. In the children with periventricular white matter injury (group 2), only 11% improved more than one level.

We admit that this is not an ideal study. It was not prospective and patients did not all enter at the same age or return for the same number of follow-up visits. Nevertheless, it is a relatively large group of children with cortical visual impairment and, in general, they

Table 2 Changes in vision from initial until the last examination

Vision change	*Patients with striate cortex damage*	*Patients with periventricular white matter damage*
No improvement	9 (21.9%)	15 (57.6%)
Improved by one level	18 (43.9%)	8 (30.7%)
Improved by two levels	11 (26.8%)	2 (7.6%)
Improved by three levels	2 (4.8%)	1 (3.8%)
Improved by four levels	1 (2.4%)	0
Improved by five levels	0	0

Table 3 Associated ocular abnormalities

Associated ocular abnormalities	*Patients with striate cortex damage*	*Patients with periventricular white matter damage*
Strabismus	5 (12.1%)	14 (53.8%)
Ocular motor apraxia/or gaze palsy	8 (19.5%)	3 (8.4%)
Nystagmus	2 (4.8%)	13 (50%)
Optic atrophy	6 (14.5%)	10 (38.4%)
Retinal disease excluding ROP	0	1 (3.8%)

were followed for a long period of time (average 5.9 years). The results of this study would seem to suggest that the visual function of children with periventricular leukomalacia may be slightly worse than those with striate cortex on the initial examination. However, the two groups are strikingly different when assessed over the long term. Children with striate cortex damage will usually show some improvement in visual function and in some cases, it is dramatic. Children with periventricular leukomalacia are much less likely to improve and if they do so, it is unlikely to be more than one level on our functional scale.

We also made note of coexisting ocular deficits that might be important in establishing the visual prognosis or understanding the nature of the visual loss in these patients. These findings are summarized in Table 3. Strabismus and nystagmus has generally been considered to be uncommon in children with cortical visual impairment.[49,50] This rule holds reasonably well for children with striate cortex injuries—only 12.1% had strabismus and 4.8% had nystagmus. However, the rule does not hold for children with periventricular leukomalacia—58.3% had strabismus and 50% had nystagmus. These differences should be of interest to those studying the possible neurologic substrates of infantile strabismus and nystagmus. In both groups, there is the confounding problem of either ocular motor apraxia or saccadic palsy in a small percentage of patients—19.5% of children with striate cortex injury and 8.4% of patients with periventricular leukomalacia. As a result of the poor saccadic eye movements seen in these children, early visual function assessment based on either 'fixation and following' eye movements or Teller acuity cards may overestimate the extent of damage to neural sensory systems. Optic atrophy, usually mild, may be seen in either group—14.5% of those with striate cortex damage and 38.4% of those with periventricular white matter damage. Optic atrophy has been noted in other studies of cortical visual impairment in children.[54,57,151,152] Whether this results from trans-synaptic degeneration of optic axons as a result of bilateral damage to the striate cortex and/or optic radiations, as some others have suggested,[57,151] will be discussed in the next section. In any case, when present, optic atrophy obviously adds to the visual disability of the child with cortical visual impairment.

Recall that Holmes insisted that injury to the visual cortex in adults resulted in a permanent scotoma. If this is so, why do some children with cortical visual impairment improve over time? Moreover, why is it that those with striate cortex damage are more likely to improve than those with optic radiation lesions? These questions led us back to the investigations of visual recovery after striate cortex damage and the investigators who have followed Holmes.

Mechanisms of visual recovery in children with cortical visual impairment

There are several possible reasons as to why infants with some forms of cortical visual impairment seem to improve over time. One reason may be simply that the normal maturation of visual systems that occurs in normal infants allows residual visual potential in these brain-damaged children to become apparent over time.[153,154] Another is that the damage to the visual cortex and/or optic radiations is usually incomplete in these children. Thus, residual visual function can be attributed to the residual intact functioning visual cortex and radiations.[50] Yet, most investigators who study these children seem to believe that some unique mechanism of plasticity of the brain in infants is an important factor in the apparent visual recovery that occurs in many of these children.[51,54,55,62] In order to understand what mechanisms may account for this apparent plasticity of infant visual brain, it is important to detail both our current understanding of adult recovery mechanisms involved in visual cortex injuries and the recent animal models that have specifically addressed infant visual cortex ablation.

Holmes was not the only physician to study visual fields of injured soldiers in the First World War. In 1917, George Riddoch,[155] a Captain in the Royal Army Medical Corps, described 10 patients with occipital cortex injuries who were able to perceive motion within their scotomas.[155] This led Riddoch to believe that 'movement may be recognized as a special visual perception separate and in addition to other perceptions'. Riddoch's findings were immediately challenged by Holmes.[42] Nevertheless, other investigators subsequently verified Riddoch's observations.[156,157] Although the mechanism of Riddoch's phenomenon is not established, it has been attributed to either preserved islands of visual function within the striate cortex[158] or extrastriate systems bypassing the injured visual cortex.[157,159] The latter explanation seems to have recently gained support from experimental findings. In any case, although the Riddoch phenomenon is of interest, it has never been suggested that it accounts for significant useable visual function following visual cortex injury in adults.

In the 1970s, studies by several different investigators began to suggest that cortically blind adults can 'see' considerably more than motion in their blind fields.[44–47,160–162] The term 'blindsight' was introduced to describe this phenomenon.[45,46] The term implies that the preserved visual function occurs below the level of visual

awareness in these patients.[163] The original studies were criticized by some authorities who felt that the residual visual function reported in these adult patients with striate cortex injuries could be accounted for by residual islands of functioning cortex and/or light scatter during the experiments.[159,164] However, control experiments involving blind spot stimulation[165] as well as improved fixation controls have made these explanations less likely to be valid.[45] Moreover, functional imaging studies of some of these patients have failed to reveal residual striate cortex activity.[166–168] It would appear, therefore, that in a small number of trained adults with visual cortex injury, preservation of the ability to detect stimulus presence,[169] target displacement,[170] direction of motion,[171] orientation,[165] or object discrimination[44] can be demonstrated. Studies in monkeys and humans have demonstrated that 'blindsight' exhibits a learning effect with increased accuracy as the result of extensive training.[172] It is unclear whether 'blindsight' can be used for visual rehabilitation of visual cortex-injured adult patients.[172–176]

Both Munk[19] and Schäfer[25] reported that adult monkeys and dogs showed some residual function following ablations of the visual cortex. In general, they found that more visual function was apparent in dogs than monkeys. This species-specific response to visual cortex injury is important when we review the experimental literature now available on visual cortex ablation studies. During the last two decades, investigators have detailed visual cortex injuries in adult and infant animals and the difference in their visual recovery.[177–182] There is virtually unanimous agreement that visual recovery in infant animals with visual cortex ablation is significantly more extensive and complex than that occurs in adult animals.

In cats, there are pronounced functional and anatomical differences between animals that experienced visual cortex ablation as neonates and those that undergo this as adults. Neonatal lesions of the primary visual cortex in cats lead to significant changes in the organization of visual pathways including severe retrograde degeneration of retinal ganglion cells.[183] If kittens undergo visual cortex ablation (up to the age of 2 weeks), there will be a 78% loss of retinal ganglion cells of the x/beta class, whereas visual cortex ablation in adult cat results in only a 22% loss of x/beta cells.[183,184] It is interesting to note that if one eye is enucleated in the neonatal cat at the time of visual cortex ablation, the remaining eye does not suffer a loss of ganglion cells of the x/beta class and the ganglion cells retain the response properties of striate neurons.[185]

At the cortex level, most of the adaptive changes seem to take place in the posteromedial lateral suprasylvian (PMLS) cortex. Anatomical studies with both anterograde and retrograde tracing methods reveal an increased projection from the retina through the thalamus to the posteromedial lateral suprasylvian extrastriate visual areas of cortex in the damaged hemisphere of cats with a neonatal visual cortex ablation.[178–181,186] No such enhanced projections are seen in cats who undergo visual cortex ablation as adults. Single-cell neurophysiological studies indicate that physiological compensation is present in the posteromedial lateral suprasylvian cortex and these cells developed normal receptive field properties.[187,188] However, these cells in the posteromedial lateral suprasylvian cortex do not acquire the response properties of the striate neurons that were damaged (high spatial frequency tuning and low contrast threshold).[187,188] Nevertheless, the data in experimental animals seem clear. An incomplete, but nonetheless impressive, compensation takes place primarily in the posteromedial lateral suprasylvian cortex of cats that undergo visual cortex ablation as neonates. No comparable compensation occurs in animals that undergo ablation as adults. Whether other areas of the cortex are also important in the visual recovery of infant cats with visual cortex ablation remains unclear.

Regrettably, less investigation of primate responses to visual cortical ablation has been completed. Moore *et al*[189] studied monkeys with large unilateral surgical ablations of striate cortex, sustained either in adulthood or at 5–6 weeks of age.[189] They then trained the animals on ocular motor and localization tasks. They tested the 'blind' field of these monkeys 2–5 years after the ablation had been performed. Monkeys with lesions sustained in adulthood were largely unable to detect stimuli in the 'blind' field. Monkeys with lesions of striate cortex made in infancy, however, showed residual detection capacity in the 'blind' field at the beginning of testing and improved dramatically during repeated testing. In a subsequent experiment, these same investigators showed that Macaque monkeys who undergo neonatal visual cortex ablation can also detect the direction of a moving target in the 'blind' field.[190]

Almost nothing is known about the underlying neuroanatomical substrates responsible for recovery from visual cortex damage in adult or neonatal experimental primates. Rodman *et al*[191] did demonstrate in adult Macaques that after ablation of the visual cortex, neurons in the area MT of the peristriate cortex still respond appropriately albeit less robustly and they retain direction selectivity. This would suggest that at least motion detection can be processed without striate cortex via pathways of the extrageniculostriate system from the thalamus directly to area MT.[191] Whether this explains the Riddoch phenomenon in man is yet to be determined.

The compensatory nature of the posteromedial lateral suprasylvian cortex has been conclusively demonstrated in cats but the possibility that it plays a similar compensatory role in primates who undergo comparable neonatal visual cortex damage has recently been challenged.[192,193]

Obviously, further investigations of the systems that are responsible for the superior recovery of infant primates with visual cortex injury will be extremely important in understanding the mechanisms that may be responsible for the visual 'recovery' in some children with cortical visual impairment. Nevertheless, a few conclusions can be drawn from the studies that have been thus far completed: (1) Infant animals show a much more extensive 'recovery' from visual cortex injury than adults do. This is true in all species studied. (2) If the mechanisms of recovery in human infants were similar to those of cats (a very big assumption), one would expect babies with striate cortex damage to have a better recovery than those with optic radiation damage since the retino-thalamic projections to the suprasylvian cortex would be damaged along with the optic radiation injury. Whether coexisting corpus callosal thinning in periventricular leukomalacia might also adversely affect visual outcome is less clear.[194,195] (3) In all studies, a considerable recovery period is necessary before the extent of visual recovery from visual cortex ablation is seen. In most experiments, training seems to benefit both adults and infants—at least in cats.[196] Training also seems to be beneficial to infant monkeys but it has not been shown to be effective for adult monkeys who experience visual cortex injury. (4) If the cat model of recovery applied directly to human infants, 100% of children who suffer significant striate cortex damage at birth should have easily detected optic atrophy. The fact that this is not the case should temper our enthusiasm for accepting all details of the current animal models of recovery from visual cortex ablation and applying them directly to the clinical situation of the child with cortical visual impairment.

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